REMARKS

Status of the Claims.

Claims 1-18, 38, 39, 49-51, and 54-62 are pending with entry of this amendment, no claims being cancelled and no claims being added herein. Claims 1, 38, and 47 are amended herein. These amendments introduce no new matter. Support is replete throughout the specification (*e.g.*, in the examples and claims as filed).

Objections to the specificaiton.

The specification was objected to because of an alleged erroneous citation on page 45, lines 12-17. The specification has been amended herein to eliminate this reference thereby obviating this objection.

The specification was also objected to because of the use of trademarks on page 63, line 29 and page 66, line 29. The specification is amended herein to comply with the requirements of M.P.E.P. §608.01(v) thereby obviating this objection.

35 U.S.C. §101

Claims 38-39 were rejected under r35 U.S.C. §101 as allegedly lacking utility. In particular the Examiner argued that the claims are inoperative because it is not possible to determine the statistical significance of two single samples. Applicants traverse.

Where an underlying distribution of a particular parameter (*e.g.* YKL-40 level) is determined the statistical significance of a subsequent sample can readily be ascertained. For example, "a normal, unskewed curve will have 34% of the cases between the mean and 1 standard deviation above or below the mean; 68% of cases between 1 standard deviation above and 1 below the mean; 95.5% of cases will be within two standard deviations of the mean." (*see* Exhibit A: copy of http://www.musc.edu/dc/icrebm/statisticalsignificance.html). Thus, for example, if a sample is taken that deviates from the mean by more than two standard deviations, it may be concluded that that difference is significant at the 95% confidence level.

Claims 38 and 39 are thus fully operable and the rejection under 35 U.S.C. §101 should be withdrawn.

35 U.S.C. §112, First Paragraph Enablement.

Claims 1-18 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled (Office Action paragraph 9). In particular the Examiner alleged that "one cannot extrapolate the teaching of the specification to the enablement of the claims because Tockman *et al.* 1992 *Cancer Res.*, 52: 2711s-2718 teach considerations necessary in bringing an [sic] cancer biomarker **to successful clinical application**". [emphasis added]

Claims 47m 49-51, and 54-62 were rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not establish an nexus between conditions other than cancer and cancer with respect to elevated YKL-40 levels.

Claims 1-18, 49-41, and 54-62 were rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not teach "which normal healthy human" is to be considered for the comparison (Office Action paragraph 11).

Claims 38-39 were rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not teach "which normal healthy mammal" is to be considered for the comparison (Office Action paragraph 12).

Claims 1-18, 38, 39, 49-51, and 54-62 were additionally rejected under 35 U.S.C. §112, first paragraph, as the specification allegedly does not provide enablement of the methods in the plethora of cancers claimed in claims 1, 38, and 47 (Office Action paragraph 13).

Applicants respectfully traverse.

In making the rejection under 35 U.S.C. §112, first paragraph, the Examiner applies an incorrect legal standard. In overturning a rejection under 35 U.S.C. §112, first paragraph, the Court of Appeals for the Federal Circuit expressly stated:

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, **necessarily** includes **the expection of further research and development.** The stage at which an invention in this field becomes useful is **well before it is ready to be administered to humans**. [emphasis added] *In re Brana* 34 USPQ2d 1436, 1442 (Fed. Cir. 1995)

The Court also quoted *In re Krimmel* 292 F. 2d 948, 953 (CCPA 1961) stating:

> We hold as we do because it is our firm conviction that one who has taught the puyblic that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, **even though it may eventually appear that the compound is without value in the treatment of humans.** [emphasis added]

Similarly, in In re Joyce A. Cortright 49 USPQ2d 1464 (Fed. Cir. 1999) the court stated:

> ("[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as in compliance with the enabling requirement of the first paragraph of 112 unless there is reason to doubt the objective truth of the statements** contained therein which must be relied on for enabling support."). The PTO may establish a reason to doubt an invention's asserted utility when the written description "suggest[s] **an inherently unbelievable undertaking or involve[s] implausible scientific principles**." Brana, 51 F.3d at 1566, 34 USPQ2d at 1441; see also In re Eltgroth, 419 F.2d 918, 164 USPQ 221 (CCPA 1970) (control of aging process). Treating baldness was once considered an inherently unbelievable undertaking. See In re Ferens, 417 F.2d 1072, 1074, 163 USPQ 609, 611 (CCPA 1969); In re Oberwener, 115 F.2d 826, 829, 47 USPQ 455, 458 (CCPA 1940).

In short the Court has indicated that the PTO's standard for meeting its burden of providing a "reason to doubt the objective truth of the statements contained" in the application to support an enablement rejection under USC 112, first paragraph **is the same standard as for establishing lack of utility under USC 101** (applicant's claimed invention "suggests an inherently unbelievable undertaking or involves implausible scientific principles.").

In the instant case, Applicant's invention is neither inherently unbelievable nor involved implausible scientific principles. To the contrary, as recognized by the Examiner, the specification expressly teaches:

1) Elevated YKL-40 levels correlates to decreased survival in patients with breast cancer.

2) A strong association between short survival and high pereoperative YKL-40 levels in colorectal cancer patients.

3) A relation between serum YKL-40 level and Dukes' stage in colorectal cancer patients.

4) Elevation of YKL-40 levels in prostate cancer.

5) Elevation of YKL-40 levels in small cell lung carcinoma patients.

Moreover, these observations are based on human data, not animal models.

The specification teaches how to detect and measure YKL-40 levels. In addition, the specification indicates typical YKL-40 levels in normal and diseased subjects. The specification thus clearly teaches one of skill how to make and use the invention.

In view of the foregoing, the specification clearly teaches one of skill how to make and use the claimed invention. Moreover, Applicants have provided extensive human data in support of the claimed invention. Accordingly the invention is neither "inherently unbelievable' nor "involves implausible scientific principles." The Examiner's comments regarding the "considerations necessary in bringing an [sic] cancer biomarker **to successful clinical application**" are simply not applicable to analysis of the validity of the claims under 35 U.S.C. §112, first paragraph (*see, e.g. In re Brana supra*).

In view of this, the Examiner has failed to make her *prima facie* case, and the rejection of the pending claims under 35 U.S.C. §112, first paragraph, should be withdrawn.

With respect to the Examiner's allegations regarding a nexus between conditions other than cancer and cancer with respect to elevated YKL-40 levels, Applicants submit there is no requirement to establish such a nexus. As indicated above, Applicants have demonstrated a relationship between cancer diagnosis/prognosis and elevated YKL-40. Applicants have shown how to measure and assess YKL-40 levels. The Examiner has failed to show that the claimed invention is "inherently unbelievable' or "involves implausible scientific principles."

If it is the Examiner's contention that having measured elevated YKL-40 one or skill would not be able to distinguish between cancer and some other disease state, Applicants note that like any other assay for a disease state, the assays of this invention are typically performed in the context of a differential diagnosis. Reflecting this the independent claims are are amended to clarify that the the assay provides an **indicator** (indication), in this instance, of cancer diagnosis/prognosis and use of such information in the context of a differential diagnosis or evaluation of a particular treatment regimen is routine to those in the medical profession.

The claimed invention is thus commensurate in scope with the disclosure and the examples provided therein, and no undue experimentation is required to practice the claimed method.

Accordingly, the rejection of the claims under 35 U.S.C. §112, first paragraph, on these grounds should be withdrawn..

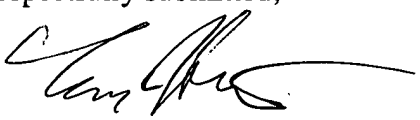
With respect to the Examiner's comments regarding the "normal healthy human" it is noted that the independent claims are amended to recite "normal healthy humans" or "normal healthy mammals" as appropriate to clarify that the comparison is with a typical baseline (control) determination. Again, Applicants have offered a wealth of data establishing the efficacy of YKL-40 as a diagnostic/prognostic marker. Moreover, legal precedent indicates that to support a rejection under 35 U.S.C. §112, first paragraph, the Examiner must establish that the claimed invention "suggests an inherently unbelievable undertaking or involves implausible scientific principles." This is simply not the case and the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. Should the Examiner seek to maintain the rejections, Applicants request a telephone interview with the Examiner and the Examiner's supervisor.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3513.

QUINE INTELLECTUAL PROPERTY LAW
GROUP, P.C.
P.O. BOX 458
Alameda, CA 94501
Tel: 510 337-7871
Fax: 510 337-7877

Respectfully submitted,



Tom Hunter
Reg. No: 38,498

Exhibit A

MUSC
MEDICAL UNIVERSITY OF SOUTH CAROLINA
Doctoring Curriculum

ICR EBM Home Page
EBM Glossary
Clinical Trials
Diagnostic Tests
Bias
EBM Terms
Statistical Significance
Epidemiology
Table of Contents
EBM Concepts
EBM Resources
Search the Internet
MUSC Find a Person
MUSC Library
MUSC Home Page

Statistical Significance

Inferential Statistics: Determines how likely a given result occurred by chance alone. Since we can rarely study an entire population, we study a sample of the population and by inference apply that result to the entire population.

Null Hypothesis: The proposal that **no difference** exists between groups or that there is **no association** between risk indicator and outcome variables. If the null hypothesis is true then the findings from the study are the result of chance or random factors. The overall purpose of a typical study is to "reject the null hypothesis." Another example: there is less than a 1 in 20 chance that the differences between treatments seen in this trial could have occurred by chance; less than a 1 in 20 chance that the null hypothesis is true.

Chance: Random variation. Difference between the outcomes from a sample of the population and the true value obtained from looking at the outcomes from the entire population. Statistical methods are used to estimate the probability that chance alone accounts for the differences in outcomes.

Clinical vs. Statistical Significance: Statistical significance means the likelihood that the difference found between groups could have occurred by chance alone. In most clinical trials, a result is statistically significant if the difference between groups could have occurred by chance alone in less than 1 time in 20. This is expressed as a p value < 0.05. Remember that a trivial difference can have a very low p value if the number of subjects is large enough! Clinical significance has little to do with statistics and is a matter of judgment. It answers the question "Is the difference between groups large enough to be worth achieving?" Studies can be statistically significant yet clinically insignificant.

Level of Significance: The probability of incorrectly rejecting the null hypothesis, i.e. saying that there is a difference between two groups when actually there is none. Otherwise known as the probability of

Type I error. By convention, the level of significance is often set to a p value of 0.01 or 0.05.

***p Value*:** The measured probability of a finding occurring, i.e. rejecting the null hypothesis, by chance alone given that the null hypothesis is actually true. By convention, a *p* value < 0.05 is often considered significant. ("There is less than a 5% probability that the finding [null hypothesis rejected] was due to chance alone.")

Power: The probability of detecting an effect in the treatment vs. control group if a difference actually exists. Must also specify the size of the difference. For example, a paper describing a clinical trial with a new hypertension medication may contain the following statement - "The study had a power of 80% to detect a difference of 5 mm Hg in diastolic blood pressure between the treatment and control groups." Typical power probabilities are 80% or greater. Power = 1 - ß (see Type II Error, below)

Type I Error: Mistakenly rejecting the null hypothesis when it is actually true. The maximum probability of making a Type I error that the researcher is willing to accept is call alpha (a). Alpha is determined before the study begins. False positive conclusion. Studies commonly set alpha to 1 in 20 (=0.05).

Type II Error: Mistakenly accepting (not rejecting) the null hypothesis when it is false. The probability of making a Type II error is called beta (b). Power = 1 - b (see above). False negative conclusion. For trials the probability of a b error is usually set at 0.20 or 20% probability. A 20% chance of missing a true difference.

Testing the Null Hypothesis to Assess Efficacy of Two Treatments (e.g. drug vs. placebo)

		Truth	
		Null hypothesis is true (no difference)	Null hypothesis is not true (difference)
Decision (based on statistical test)	Accept Null Hypothesis	Correct	Type II Error (beta)
	Reject Null Hypothesis	Type I Error (alpha)	Correct 1 - beta (Power)

Standard Error of the Mean (SEM): A measure of variability. The standard error of the mean quantifies how accurately the true population mean is known. A measure of the variability of the mean of the sample as an estimate of the true value of the population mean. The larger the sample size the smaller the standard error of the mean. Used in computing confidence intervals. In a clinical trial, the larger the sample size the tighter the 95% CI is around the point estimate of the study.

Standard Deviation: A measure of variability. The standard deviation quantifies how much the values vary from each other. A measure of the spread of individual observations around the mean value of the sample. A normal, unskewed curve will have 34% of the cases between the mean and 1 standard deviation above or below the mean; 68% of cases between 1 standard deviation above and 1 below the mean; 95.5% of cases will be within two standard deviations of the mean.

Confidence Interval: Often expressed as 95% confidence intervals. Studies are performed on a sample of the population, not the whole population. Confidence intervals give us some idea of how likely the sample mean represents the population mean. Expressed as the sample mean plus and minus a specified amount. A measure of the precision of the estimate. The 95% CI is the range of values within which we can be 95% sure that the true value lies for the whole population of patients from whom the study patients were selected. Most clinical trials study a sample of the population at risk. Because a sample is a subset of a population, the mean value obtained for the sample studied may not be same as the mean value if the entire population was studied. Results from a sample population with a wider range of values will have broader confidence intervals than results from a study with a narrower range of values. Increasing the number of results (patients) within a sample population narrows the confidence intervals. The confidence interval (CI) quantifies uncertainty. Derived from the sample mean and the standard error.
Please see: Use of confidence intervals to indicate uncertainty in research findings.

Interobserver variability: Variability between observers. Do two or more radiologists give the same reading fromthe same radiograph?

Intraobserver variability: Variability by the same observer. Does a radiologist give the same reading of a radiograph when viewed on more than one occasion?

Survival Analysis: Statistical procedures for estimating survival (prognosis) in a population under study.

Cox Proportional-Hazard Model: A type of multivariate analysis that is used to identify a combination of factors that bests predicts prognosis in the group of patients. Can also test the effect of individual factors independently. Analysis used when the outcome is the time to an event. The Cox proportional hazard model is used when practical considerations preclude observing survival time in all patients being studied.

Hazard (or Hazard Rate): Probability of an endpoint. A technical name for failure rate.

Hazard Ratio: Relative risk of an endpoint at any given time.

Multivariate Analysis: An analysis where the effects of many variables are considered. Can select a subset of variables that significantly contribute to the variation in outcome.

Kaplan-Meier Curve: Used for estimating probability of surviving a unit of time. Used to develop a survival curve when not all survival times are exactly known.

Doctoring Curriculum Home Page ICR EBM Home Page Table of Contents
MUSC Library Find a Person
MUSC Home Page

Top of Page

Last Modified January 1, 2001